REMARKS

Claims 1-26 are pending in this application. Claims 11 and 22 are canceled. Claims 1,7, 12, 16, 18, 23 and 26 are amended. Claims 1-26 have been rejected. Please enter the amendments set forth above and the following remarks into the record.

I. Rejection of Claims Under 35 U.S.C. 112

Claims 1-26 stand rejected as failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, Applicants have added the word "comprising" between "molecule" and the colon, the word "identify" was changed to "identifying", and the word "media" as changed to "medium", and step (e) where the cells secrete the proteinaceous molecule was added.

The word "media" was also changed to "medium" in claims 16, 18 and 23.

The term "excrete" was changed to "secrete" in claims 18 and 23.

Claim 7 was changed to depend on claim 6. The Examiner also claims 7 and 21 because "bioselection by antibiotic resistance would not work in a mammalian cell since antibiotics already have no effect on mammalian cells." However, as highlighted in the specification sheet for Blasticidin S HCl, Blasticidin is used for selection in mammalian cell lines (see Attachment A).

II. Rejection of Claims Under 35 U.S.C. 103(a)

The Examiner rejected claims 1-26 under 35 U.S.C. 103(a).

Independent claims 1, 18 and 23 were rejected as being unpatentable over Rai et al. and Verma et al. in view of Spaulding et al. and Schwartz et al. (US Patent 5,026, 650) and further in view of Anderson et al. and others.

A. Rai et al. and Verma et al.

Applicants agree with the Examiner that Rai et al. and others teach that mammalian cells are the best choice for producing clinically efficacious therapeutics of highly post-translated proteins. Although many investigators have recognized the superiority of using mammalian cells, the literature

overwhelmingly teaches against the general use of mammalian cells by setting out the specific disadvantages in using these cells. The major disadvantages taught are the slow growth of mammalian cells, the low density of mammalian cells in culture and the low product yield. Thus, most companies that commercially produce proteinaceous therapeutics will only choose mammalian cells if there is no other viable choice. In fact, the difficulty of working with mammalian cells has necessitated the expenditure of much time, energy and money in improving the production of therapeutics in yeast and insect cells as potential replacements for the mammalian system.

For example, Rai et al. (page 1124 at the top of the page lists several of the factors contributing to the popularity of insect cells, as opposed to mammalian cells, in the production of proteinaceous therapeutics. Rai et al. (page 1124 under the heading Mammalian cells) specifically teaches away from using mammalian cells except as a final resort. Rai et al. state "If product authenticity is absolutely essential for clinical efficacy, **then despite the many shortcomings**, a mammalian host is the only choice . . .." They also express the general view of many researchers in their statement that "mammalian expression techniques are time consuming and **much more difficult to perform on a large scale**."

Verma et al. also compares different expression systems. Like Rai et al. they point out the value of mammalian cell expression and discuss when to choose to express a recombinant protein in mammalian cells and how one might go about doing it.

The Applicants also recognize the advantages, and often the necessity, of using mammalian cell expression in the production of mammalian proteins. The present invention recognizes and address the problems associated with mammalian cultures such as low cell density and low product concentration. (See the discussion below under Anderson et al.)

As a result of the problems of using mammalian cell cultures, most investigators try to find a non-mammalian system to produce genetically engineered proteins. By minimizing the problems encountered in using mammalian cell cultures, the present invention teaches that when one desires to produce a mammalian protein that undergoes major post-translational modification that one should not avoid the mammalian system, but in fact should specifically select a mammalian cell type that is known to produce the desired protein.

B. Spaulding et al. and Schwartz et al.

Spaulding et al. and Schwartz et al. teach the use of a rotating bioreactor to produce both low shear and low gravity environments for cell culture. In fact, Spaulding et al. teaches recombinant protein production in insect cells. However, insect cells are very different from mammalian cells and do not have the same problems of low cell density and low recombinant product concentration. Although mammalian and human cells have been shown to grow in horizontally rotating culture vessels HARVs), genetically engineered mammalian cells are not grown in HARVs for their production of recombinant proteins because the HARVs described do not address the issue of low product concentration. The present invention teaches a solution to this issue.

The present application teaches the use of a membrane carrier assembly as a means of increasing cell density and of increasing product concentration.

C. Anderson et al.

The Examiner cites Anderson et al. as teaching an improvement in the rotating cell culture device of Schwartz et al. incorporating filters transversing the space within the bioreactor to subdivide the space while still permitting enhanced flow of medium containing nutrients and oxygen. However, the Anderson et al. filters do not function as the membranes taught in the present invention, nor do they solve the problems solved by the present invention.

Applicants have amended independent claims 1, 18 and 23 to recite "a membrane carrier assembly transverses a growth compartment, the membrane carrier comprising a support cylinder having a first end in communication with a fluid inlet and a second end in communication with a fluid outlet, a molecular weight cut-off membrane secured to an exterior surface of the support cylinder, and a medium circulation chamber between the exterior surface of the cylinder and an interior surface of the membrane, the chamber in fluid communication with the fluid inlet and the fluid outlet."

Although the Examiner acknowledges that Anderson et al. do not teach their filters specifically having a cutoff of a particular molecular weight, he found that it would have been obvious to one of ordinary skill in the art to select a pore size of the filters to either trap the secreted protein or let it through to be removed by the flowing medium.

Applicants respectfully disagree with the Examiner for at least the following reasons:

1. **Anderson et al. teach a filter, not a molecular weight cut-off membrane.**

The filters are used to "define and subdivide the culture chamber and to retain the growing cells, cellular aggregates, tissues and/or organoids in the culture chamber." (See column 8, lines 65-67, and column 9, line 1). The pore size of a filter that is selected to retain cells and cellular aggregates is much larger than the pore size of a molecular weight cut-off filter designed to separate molecules based on their molecular weights.

In fact, Anderson et al. teach away from the small pore size of a molecular weight membrane such as dialysis tubing. At column 9, lines 17-20, they state that the filters should "have a porosity that allows the nutrient medium and cellular metabolic waste to travel through the filter but that will prevent the passage of cells and cellular aggregates." In addition, they state "Therefore the use of filters is preferred over dialysis membranes and the like." (See column 9, lines 1-2). Throughout the detailed description of their invention, Anderson, et al. describe the filters as larger pore size materials for retaining cell-sized particulates, rather than proteins and the molecular constituents of the medium.

2. **Molecular weight cut-off membranes would not work as an Anderson et al. filter.**

The flow of medium through the culture chamber 10 of Anderson et al. requires that the medium go from the inlet through the cell compartment and out through the outlet. (See Attachment B showing the flow patterns for the culture chamber 10). This flow pattern causes the filters to clog with particulate matter. Anderson et al. state at column 10, lines 38-42, "It is anticipated that filter 36 may periodically become clogged with cells and cellular aggregates."

The use of molecular weight membranes in the culture chamber 10 would be unworkable. To force the medium through the inlet filter and through the exit filter, where particulate matter is retained in the chamber by the filter, would become clogged very rapidly and would not provide a sufficient flow rate to keep the cells well oxygenated and in a healthy environment.

3. **Anderson et al. do not teach a medium circulation chamber.**

The present invention does not require the medium to be circulated through the membrane; instead the medium is circulated through the medium circulation chamber between the exterior surface of the support cylinder and the interior of the membrane. Thus, medium circulates through the chamber on one side of the membrane and the cells in the growth chamber are on the other side of the membrane. Instead of filtering the medium through the membrane and clogging the membrane, the circulating medium on one side of the membrane assists in preventing the clogging of the pores of the membrane. The membrane is available for perfusion of nutrients, growth factors and the like into the culture chamber and the perfusion of metabolic waste outside of the culture chamber. The selection of the molecular weight cut-off of the membrane controls the compounds going in and out of the growth chamber. This use of a medium circulation chamber provides a healthy environment for the cells that allows for higher cell densities than is generally seen in horizontally rotating culture chambers. In addition, the selective use of a molecular weight cut-off membrane for molecular weights less than the molecular weight of the therapeutic product produced by the cells allows for a significant concentration of the product. Thus, the present invention addresses two of the major problems in using mammalian expression systems- low cell densities and low product concentration.

Not one of the references cited by the Examiner utilized a culture chamber transversed by a membrane carrier assembly having a support cylinder with a molecular weight cut-off membrane secured to its exterior surface. The design of this membrane carrier assembly and the advantages of the medium circulation chamber have not been disclosed by the references cited or suggested by the references. Even though many investigators had recognized the need for using mammalian expression systems to produce efficient therapeutic proteins, no one has proposed a system like the membrane carrier assembly to address and solve the well known problems of low cell density and low product concentration.

III. Combination of References

To establish a prima facie case of obviousness there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The prior art must also teach or

suggest all claim limitations. In this case the prior art cited fails to teach or suggest all claim limitations (such as the membrane carrier assembly) of the independent claims, either alone or in combination. Therefore, the cited references would not motivate one to make or use the claimed invention with a membrane carrier assembly having a support cylinder, a molecular weight cut-off membrane, and a medium circulation chamber.

Claims 2-17 are dependent on amended claim 1, claims 19-22 are dependent on amended claim 18 and claims 24-26 are dependent on claim 23. Each dependent claim contains all of the limitations of its independent claim. Thus, the dependent claims of independent claims 1, 18 and 23 are patentably distinct from the cited references.

IV. Conclusion

In view of the foregoing amendments and remarks, it is respectfully submitted that Applicants have responded in a fully satisfactory manner to all matters at issue in the Office Action. If the Examiner has any questions or suggestions concerning the application, or feels that an interview would advance the examination process, the Examiner is requested to call the Applicant's undersigned attorney at the direct dial number printed below.

Respectfully submitted,

Elizabeth R. Hall & Associates, P.C.

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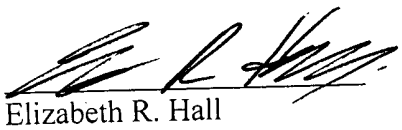

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